Comparison of the potencies of clebopride and other substituted benzamide drugs on isolated gastrointestinal tract of the guinea-pig and rat

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The substituted benzamides (*o*-anisamides or *o*-pramides) are used clinically for a variety of indications including nausea and vomiting, psychotic disturbances and divers problems associated with gastric stasis. Although the anti-emetic and tranquillizing effects are most probably related to their action in blocking dopamine receptors (Elliott et al 1977; Salazar et al 1978; Costall et al 1978), the mechanism(s) of action on the gastrointestinal tract is far from clear (Reuse 1973; Hay 1977; Bury & Mashford 1976; Massó et al 1978).

The most recently introduced substituted benzamide, clebopride (Prieto et al 1977), has been shown to be much more potent than previous members of the series as a dopamine receptor blocking agent (Roberts et al 1978; Jenner et al 1978 and references cited above), comparative data for clebopride on the gastrointestinal tract is now reported. Metoclopramide and sulpiride were chosen as representatives of earlier members of the group and the comparisons were made using isolated preparations to avoid possible interference from centrally mediated effects. Since there is substantial evidence for the involvement of 5-hydroxytryptaminergic mechanisms in the contractile response of gastrointestinal smooth muscle to substituted benzamides (Reuse 1973; Massó et al 1978), albeit as a possible consequence of the blockade of a dopaminergic interneuronal control mechanism at the level of the myenteric plexi (Massó et al 1978; Roberts 1979), 5-HT was also included in the study.

Strips of rat gastric fundus (Krebs solution, 37 °C, 5% CO_2 + 95% O_2) and portions of guinea-pig ileum and colon (Tyrode solution, 32 °C, air) were prepared and mounted in organ baths, containing appropriately gassed and temperature-controlled solutions, using standard techniques. Drugs were added to the bath in increasing doses (contact time 30 s) at 20 min intervals to avoid tachyphylaxis, and the responses were recorded isotonically via transducers connected to a microdynamometer (Ugo Basile, Milan, Italy). At the start of each experiment the tissues were made to contract maximally to acetylcholine and between-experiment variation was reduced by calculating all subsequent responses as percentages of this maximal contraction. The results are summarized in Fig. 1.

Clebopride induced dose-related contractions of all three preparations with maximal effects at concentrations between $4{\cdot}4 \times 10^{-5}$ M (stomach and ileum) and $4{\cdot}4 \times 10^{-6}$ M (colon) which ranged in magnitude from 60% (ileum) to 25% or less (stomach and colon) of the maximal responses obtained with acetylcholine. In each case, further increases in the dose resulted in a progressive decline in the contractile response. Metoclopramide also exhibited biphasic dose-response curves on the stomach and ileum preparations, although the maximal responses (at $7{\cdot}2 \times 10^{-5}$ M in each case) were smaller than those obtained with clebopride, whereas on the colon preparation it only induced very small non dose-related contractions. With sulpiride the only preparation showing measurable responses was the ileum and the maximal response (at $8{\cdot}8 \times 10^{-6}$ M) was notably smaller than that obtained with either metoclopramide or clebopride.

5-HT (10^{-8} to 10^{-2} M), like clebopride, induced dose-related contractions in all three preparations with maximal responses at concentrations of $1{\cdot}1 \times 10^{-6}$ M (stomach), $3{\cdot}2 \times 10^{-6}$ M (ileum) and $1{\cdot}1 \times 10^{-5}$ M (colon) which were about double those obtained with clebopride in all preparations. The tissue sensitivity sequence for 5-HT (ileum > stomach > colon) is therefore identical to that of the substituted benzamides, a finding which indirectly supports the possibility of involvement of 5-HT-ergic mechanisms in the induced contractile responses. The 5-HT dose-response curves were also, at least in the case of stomach and colon, clearly biphasic and with a reduction in the time interval between doses the same was true of the ileum. Although this phenomenon is best explained in terms of tachyphylaxis it is probably also related to local anaesthetic activity, especially in the case of the substituted benzamides.

Whether the 5-HT-like agonistic effect of the substituted benzamides results from a prior antagonism of inhibitory dopaminergic mechanisms remains unknown. However, the absence of significant contractile responses to domperidone, a butyrophenone shown to have antiemetic and stomach emptying properties associated with blockade of dopamine receptors peripheral to the blood-brain barrier (Reyntjens et al 1978), in all three tissues (unpublished results) is, at least superficially, difficult to reconcile with such a concept. Nevertheless, it may be more than coincidence that the weakest substituted benzamide tested, sulpiride, shares with domperidone the property of only poorly penetrating the blood brain barrier (Benakis & Rey 1976; Benakis et al 1976) and perhaps their access to gastrointestinal dopamine receptors is similarly limited. Antagonism of apomorphine-induced gastric relaxation by such drugs

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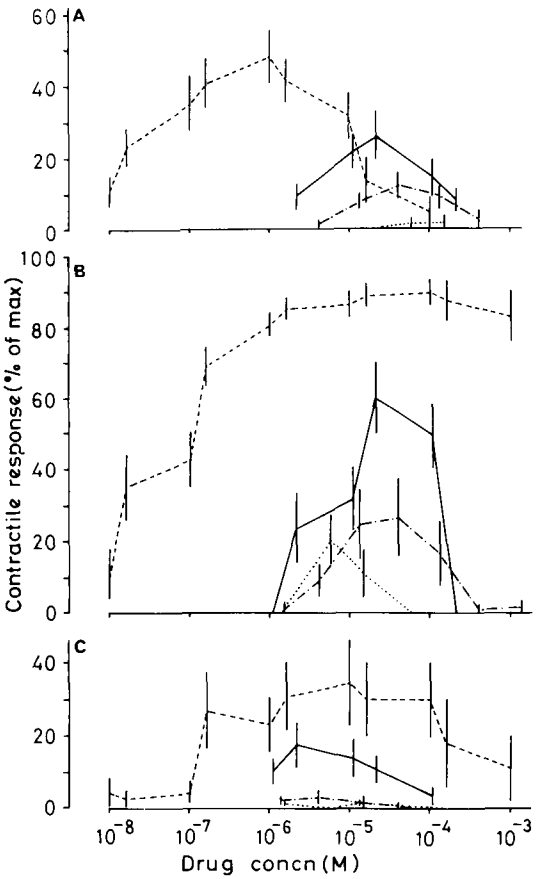

FIG. 1. Effect of increasing concentrations (M, abscissa) of clebopride acid malate (————), metoclopramide hydrochloride monohydrate (— . — . —), sulpiride (. . . . . .) and 5-HT creatinine sulphate (- - - - -) on the rat isolated fundic strip (A), guinea-pig isolated distal ileum (B) and isolated colon (C). Contractile responses (ordinate) expressed as percentages of maximal contractions induced by acetylcholine. Each point represents the mean value obtained from at least 6 preparations and the vertical bars indicate the s.e.m. In all experiments the actual dose sequence used to obtain the dose-response curves was 1, 3, 10 . . . 1000 μg^{-1} of bath fluid except that with 5-HT creatinine sulphate dosing was started at 0·01 $\mu g\ ml^{-1}$. Molar concentrations are expressed in terms of base.

in vivo (Lefebvre & Willems 1979) is not contradictory to this suggestion since such antagonism probably occurs at the level of the chemosensitive trigger zone of the area postrema, a site apparently not protected by the blood brain barrier (Cheng & Long 1974).

Alternatively, in accord with present thought on the existence of multiple receptors for dopamine and the recent suggestion that the orthopramides are selective antagonists for one of these (Kebabian & Calne 1979), the presence of more than one dopamine sensitive mechanism might be postulated for the gastrointestinal tract. In this context the recent demonstration (Cox & Ennis 1980) that dopamine-induced relaxation of the guinea-pig isolated gastroesophageal junction preparation is antagonized by domperidone but not by metoclopramide may be relevant.

In any event the present experiments have shown that at the level of the gastrointestinal tract, as in less putative central nervous system models for anti-dopaminergic activity, the potency of clebopride is greater than that of other substituted benzamide drugs.

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